which the instant application is a continuation in part, where peptide-based cofactors are disclosed.

Concerning the 35 USC 112 (par. 2) rejection of Claim 9, the Applicant respectfully traverses the Examiner's grammatical objection. The word "including" is used as a gerund in this claim. The Applicant is nevertheless sympathetic to the difficulties in parsing this claim, and has amended it.

The double patenting rejections of Claims 1,2, 5 and 6 seem to be valid.

AMENDMENTS TO THE CLAIMS

Please cancel Claims 1,2, 5 and 6.

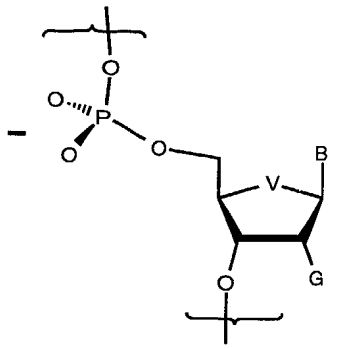
Please amend Claim 9 as follows:

9. (amended) An improvement in a method for creating a catalyst for a preselected reaction, said method comprising:
a) synthesizing a mixture of oligonucleotides from nucleotide building blocks each having a region of randomized sequence
b) incubating said mixture under conditions where oligonucleotides that catalyze said reaction undergo as a result of their catalytic activity a chemical transformation that makes them preferentially partitionable from or amplifiable to oligonucleotides in the remainder of the mixture that have diminished or none of said catalytic activity,
c) partitioning the oligonucleotides with increased catalytic activity from the other oligonucleotides in the mixture
d) amplifying the oligonucleotides having increased affinity *in vitro* to yield a mixture of oligonucleotides enriched in those with increased affinity for said target,
wherein said [the] improvement comprises:
e) including an organic cofactor during step (b) [an organic cofactor], wherein said organic cofactor carries [carrying] an organic functional group [with affinity for] that binds noncovalently to the oligonucleotides so enriched.

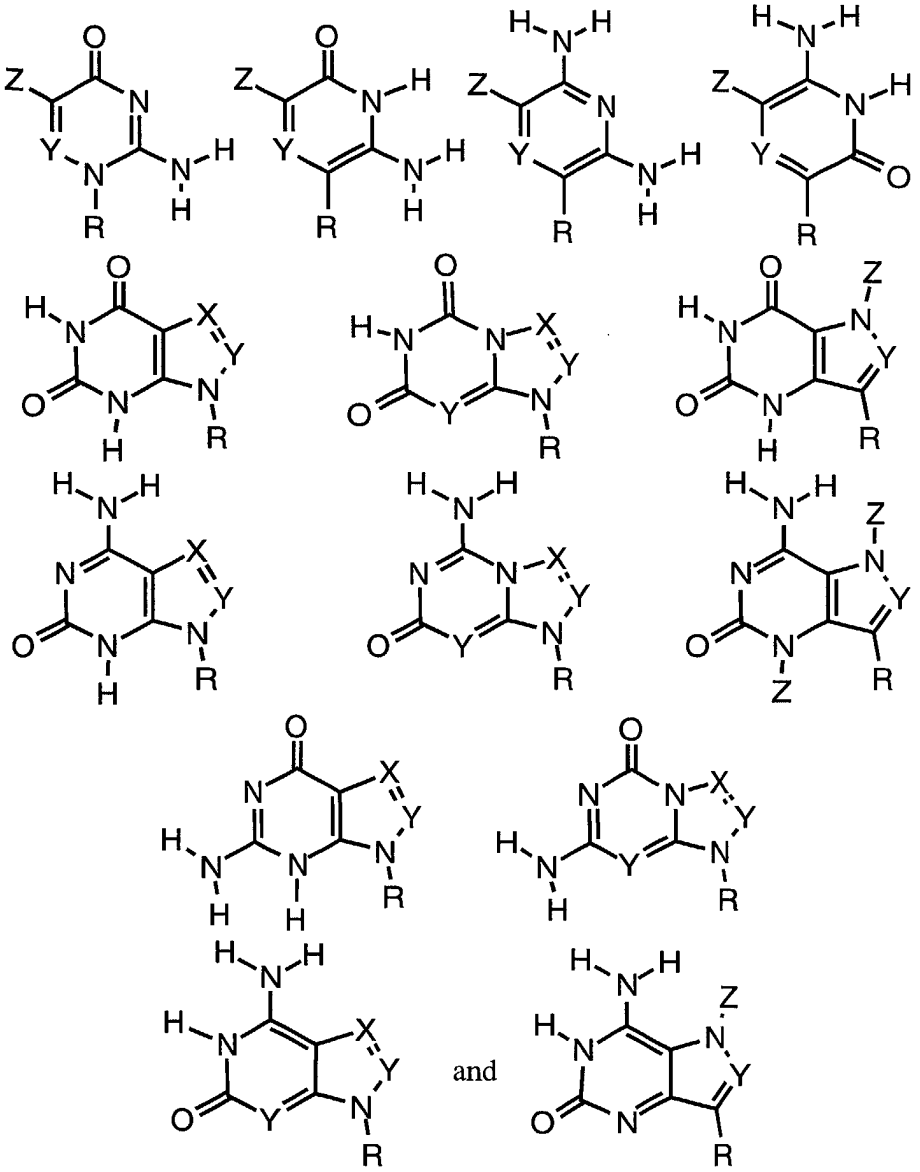
ADDITIONAL CLAIMS

Please add the following claims.

11. An oligonucleotide analog in which one or more of the constituent nucleotide units is replaced by a nucleotide analog having the formula

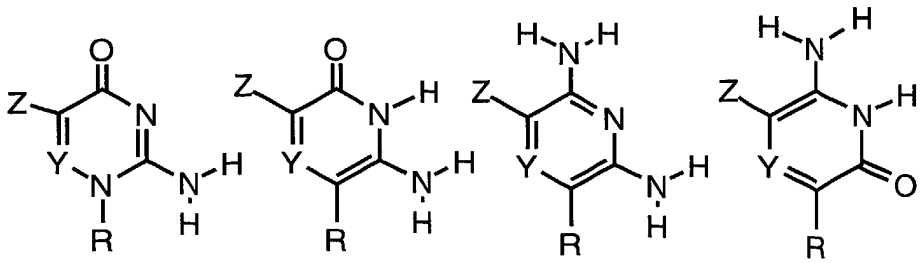


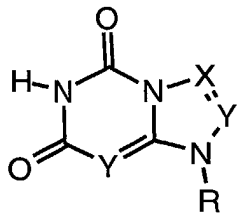
wherein
G is selected from the group consisting of -H and -OH,
V is selected from the group consisting of $-CH_2-$ or -O-,
and B is a nucleobase analog independently selected from the group consisting of,

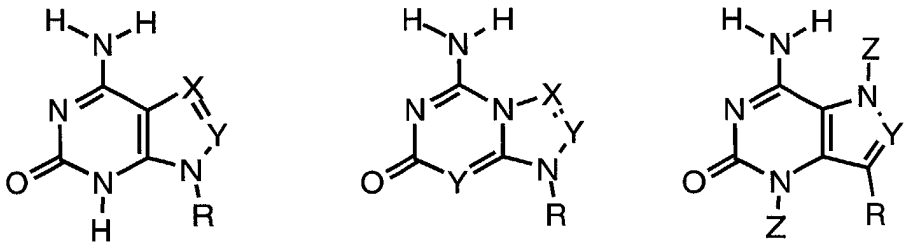


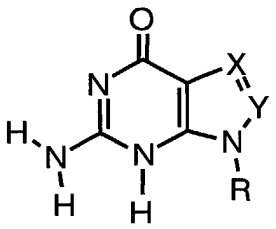
wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
X is selected from the group consisting of a nitrogen atom and a carbon atom bearing a substituent Z,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, thiol, aryl, indole, or imidazoyl group,
Y is selected from the group consisting of N or CH,
and said ring structure of said nucleobase analog comprises no more than three nitrogen atoms consecutively bonded,
and wherein said oligonucleotide analog is not a homopolymer of iso-guanine.

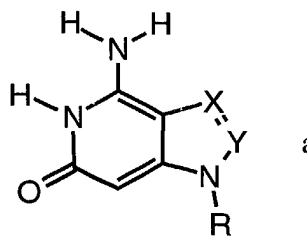
12. The oligonucleotide analog of claim 11, wherein said nucleotide analog units is selected from the group consisting of



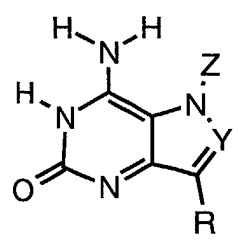






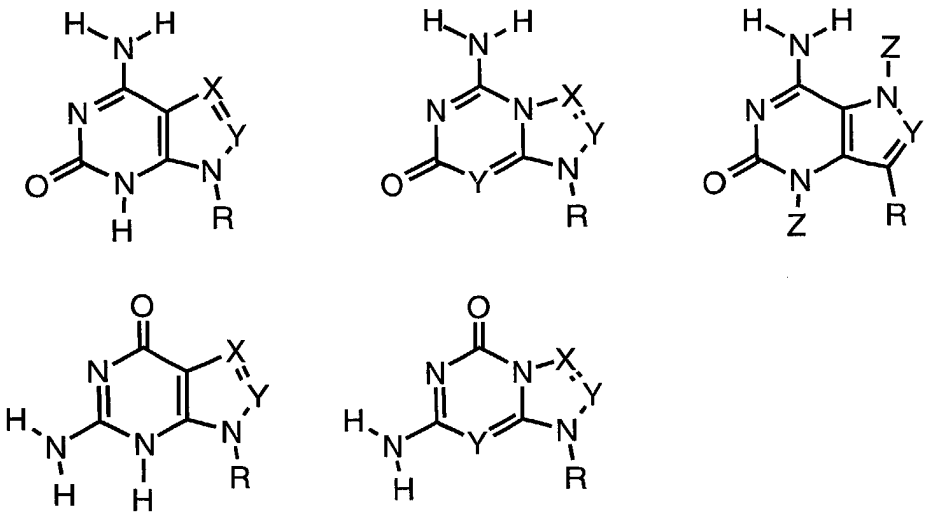


and



13. The oligonucleotide analog of claim 11, wherein the number of said nucleotide analog units is greater than one.

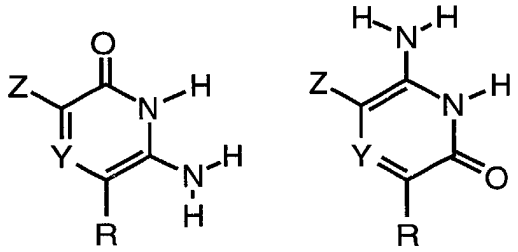
14. The oligonucleotide analog of claim 11, wherein said nucleotide analog unit is selected from the group consisting of



wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
X is selected from the group consisting of a nitrogen atom and a carbon atom bearing a substituent Z,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, thiol, aryl, indole, or imidazoyl group,
Y is selected from the group consisting of N or CH,
and said ring structure of said nucleobase analog comprises no more than three nitrogen atoms consecutively bonded.

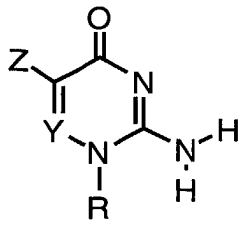
15. The oligonucleotide analog of claim 11, wherein said nucleotide analog unit is selected from the group consisting of

A cont



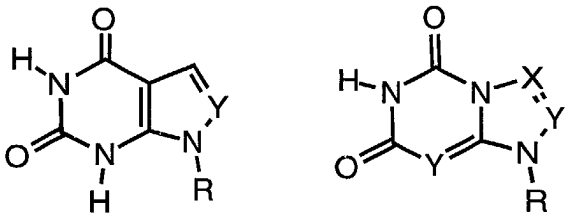
wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
X is selected from the group consisting of a nitrogen atom and a carbon atom bearing a substituent Z,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, thiol, aryl, indole, or imidazoyl group,
Y is selected from the group consisting of N or CH,
and said ring structure of said nucleobase analog comprises no more than three nitrogen atoms consecutively bonded.

16. The oligonucleotide analog of claim 11, wherein said nucleotide analog unit has the formula



wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, thiol, aryl, indole, or imidazoyl group, and Y is selected from the group consisting of N or CH.

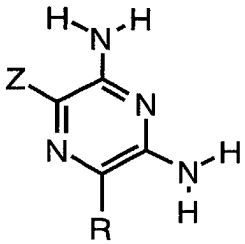
17. The oligonucleotide analog of claim 11, wherein said nucleotide analog unit is selected from the group consisting of



A cont.

wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
X is selected from the group consisting of a nitrogen atom and a carbon atom bearing a substituent Z,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, thiol, aryl, indole, or imidazoyl group, and Y is selected from the group consisting of N or CH.

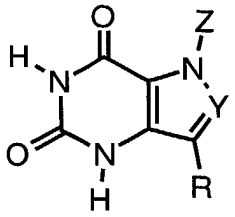
18. The oligonucleotide analog of claim 11, wherein said nucleotide analog unit has the formula



wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, chloro, thiol, aryl, indole, or imidazoyl group,

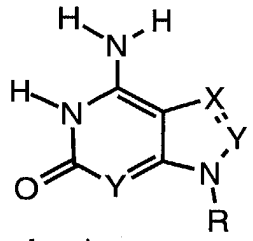
and Y is selected from the group consisting of N or CH.

19. The oligonucleotide analog of claim 11, wherein said nucleotide analog unit has the formula



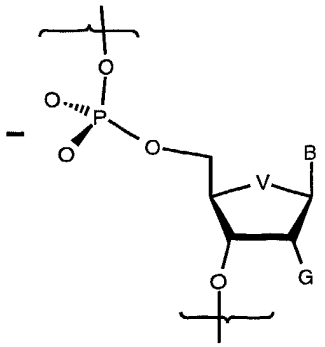
wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, chloro, thiol, aryl, indole, or imidazoyl group,
and Y is selected from the group consisting of N or CH.

20. The oligonucleotide analog of claim 11, wherein said nucleotide analog unit has the formula



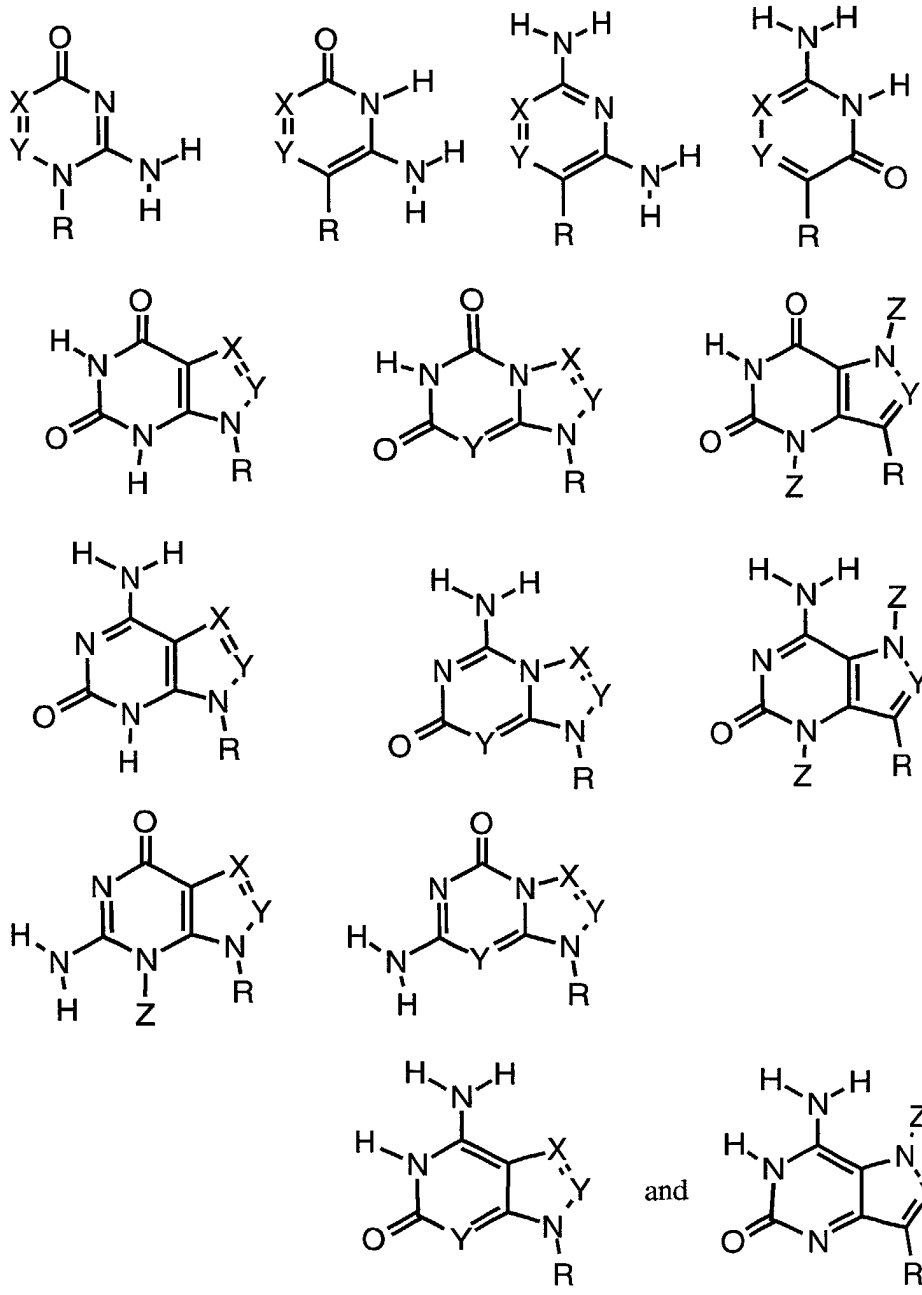
wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, chloro, thiol, aryl, indole, or imidazoyl group,
and Y is selected from the group consisting of N or CH.

21. A method for incorporating into a DNA or RNA oligonucleotide chain one or more nucleotide analog units having the formula



wherein

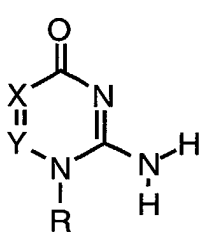
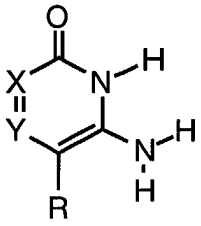
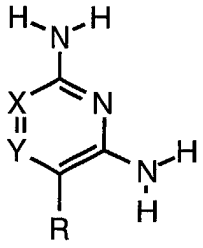
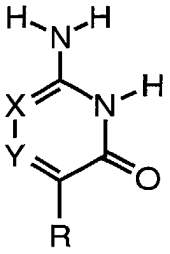
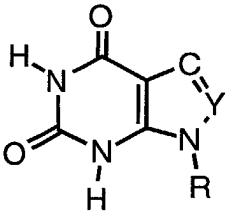
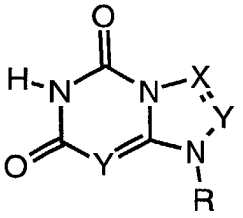
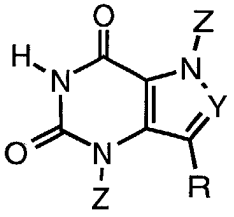
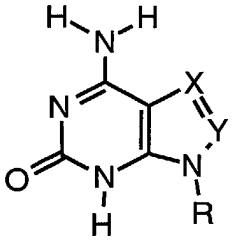
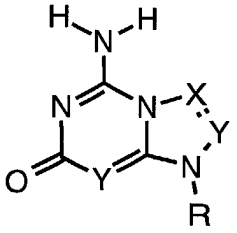
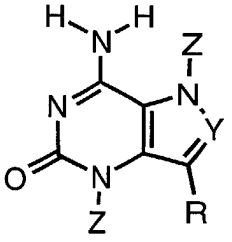
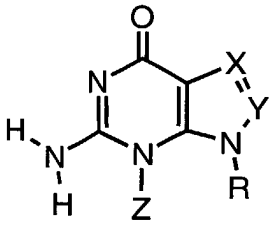
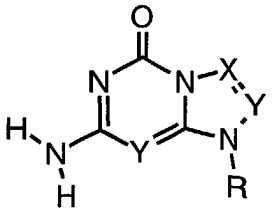
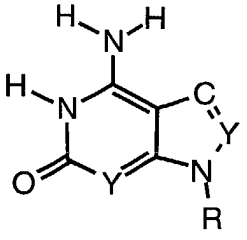
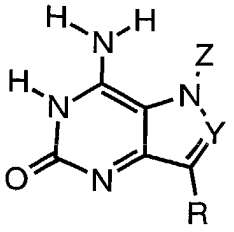
G is selected from the group consisting of -H and -OH,
V is selected from the group consisting of $-CH_2-$ or -O-,
and B is a heterocycle independently selected from the group consisting of,



wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
X is selected from the group consisting of a nitrogen atom and a carbon atom bearing a substituent Z,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, thiol, aryl, indole, or imidazoyl group,

Y is selected from the group consisting of N or CH,
and said ring structure of said heterocycle comprises no more than three nitrogen atoms consecutively bonded, that consists of synthesizing a template that is an oligonucleotide containing one or more nucleotide analogs as subunits bearing the Watson-Crick complement of said heterocycle or heterocycles, dissolving this template in buffered aqueous solution, adding to the solution triphosphates of the deoxynucleoside or nucleoside analog incorporating said heterocyclic base, adding to this solution a solution of a polymerase, wherein said polymerase is suitable for use in a polymerase chain reaction.

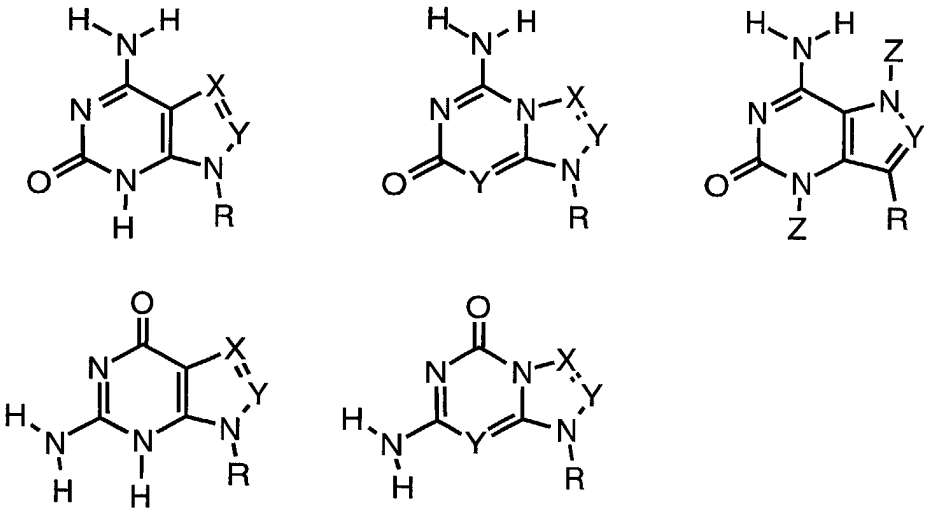
22. The method of claim 21 wherein said heterocyclic base is selected from the group consisting of














and


-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
X is selected from the group consisting of a nitrogen atom and a carbon atom bearing a substituent Z,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, thiol, aryl, indole, or imidazoyl group,
Y is selected from the group consisting of N or CH,
and said ring structure of said heterocycle comprises no more than three nitrogen atoms consecutively bonded, that consists of synthesizing a template that is an oligonucleotide containing one or more nucleotide analogs as subunits bearing the Watson-Crick complement of said heterocycle or heterocycles, dissolving this template in buffered aqueous solution, adding to the solution triphosphates of the deoxynucleoside or nucleoside analog incorporating said heterocyclic base, adding to this solution a solution of a polymerase, wherein said polymerase is a DNA polymerase, an RNA polymerase, or a reverse transcriptase.

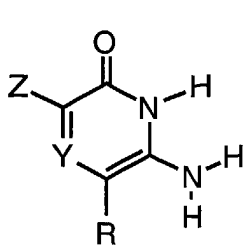
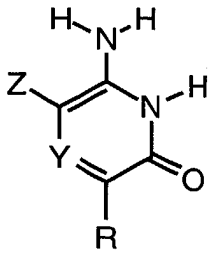
23. The method of claim 21, wherein the number of said nucleotide analog units is greater than one.

24. The method of claim 21, wherein said nucleotide analog unit is selected from the group consisting of



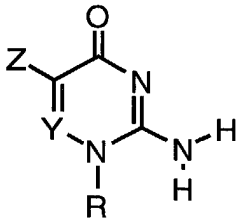
wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
X is selected from the group consisting of a nitrogen atom and a carbon atom bearing a substituent Z,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, thiol, aryl, indole, or imidazoyl group,
Y is selected from the group consisting of N or CH,
and said ring structure of said nucleobase analog comprises no more than three nitrogen atoms consecutively bonded.

25. The method of claim 21, wherein said nucleotide analog unit is selected from the group consisting of

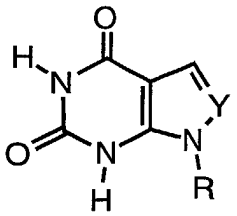
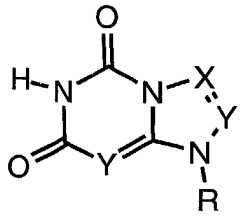
wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, thiol, aryl, indole, or imidazoyl group, and Y is selected from the group consisting of N or CH.

26. The method of claim 21, wherein said nucleotide analog unit has the formula



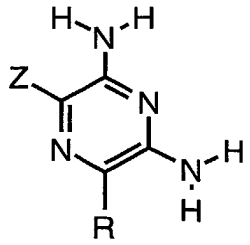
wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, thiol, aryl, indole, or imidazoyl group, and Y is selected from the group consisting of N or CH.

27. The method of claim 21, wherein said nucleotide analog unit is selected from the group consisting of

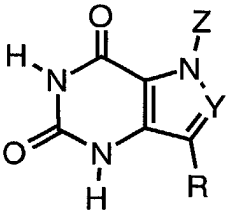
wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
X is selected from the group consisting of a nitrogen atom and a carbon atom bearing a substituent Z,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, thiol, aryl, indole, or imidazoyl group, and Y is selected from the group consisting of N or CH.

28. The method of claim 21, wherein said nucleotide analog unit has the formula



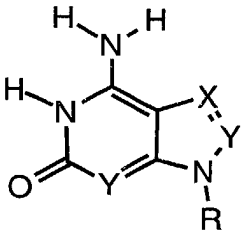
wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
and Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, chloro, thiol, aryl, indole, or imidazoyl group.

29. The method of claim 21, wherein said nucleotide analog unit has the formula



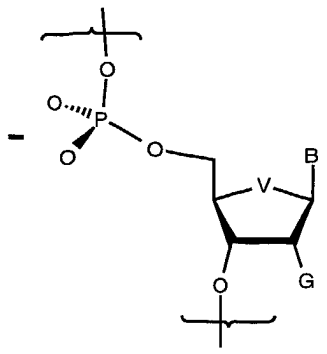
wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, chloro, thiol, aryl, indole, or imidazoyl group,
and Y is selected from the group consisting of N or CH.

30. The method of claim 21, wherein said nucleotide analog unit has the formula



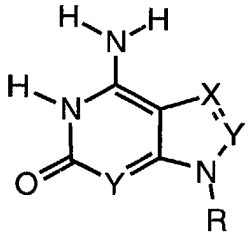
wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
X is selected from the group consisting of a nitrogen atom and a carbon atom bearing a substituent Z,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, chloro, thiol, aryl, indole, or imidazoyl group,
and Y is selected from the group consisting of N or CH.

31. A method of synthesizing a duplex of two oligonucleotides wherein said duplex pairs one or more thymidine or uridine nucleotides opposite one or more nucleotide analog units having the formula

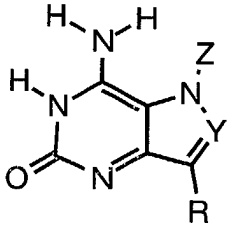


wherein

G is selected from the group consisting of -H and -OH,
V is selected from the group consisting of $-CH_2-$ or -O-,
and B is a heterocycle independently selected from the group consisting of,



and



wherein
-R designates the point of attachment of the heterocycle to the oligonucleotide analog,
X is selected from the group consisting of a nitrogen atom and a carbon atom bearing a substituent Z,
Z is a moiety selected from the group consisting of an unfunctionalized lower alkyl, alkynyl, or alkyl-alkynyl chain of 1-4 carbon atoms, or a alkyl, alkenyl, alkynyl, alkenyl-alkyl, or alkyl-alkynyl chain bearing an amino, carboxyl, hydroxyl, chloro, thiol, aryl, indole, or imidazoyl group,
and Y is selected from the group consisting of N or CH.

COMMENTS ON ADDITIONAL CLAIMS

It has come to the Applicant's attention that two coworkers of mine gave presentations at two meetings of the American Chemical Society. The first was at the September 1988 meeting of the American Chemical Society in Los Angeles, where diaminopyridine as a riboside may have been disclosed as an unnatural nucleotide composition of matter. The second was at the April 1989 meeting of the American Chemical Society in Dallas Texas, where an oligonucleotie containing a single 2'-deoxyisocytotosine might have been disclosed, as well as the enzymatic incorporation of 2'-deoxyisoguanosine using the Klenow form of E. coli DNA polymerase I, AMV reverse transcriptase and T7 RNA polymerase. These presentations were prepared without the Applicant's involvement, and the only information that the Applicant has concerning these presentations is contained in the two abstracts that are enclosed with this response as a supplment to the information disclosure previously filed.

The Applicant does not know whether, or the extent to which, these abstracts might be cited as prior art with respect to parts of material covered in the instant patent application. Diaminpyridine is now known not to be an effective heterocycle in these systems, as it is too

readily oxidizable. Further, 2'-deoxyisoguanosine is not the preferred heterocycle in these systems because of its ready deamination.

Further, the Applicant remains concerned that the prior art that he disclosed in the first and various subsequence parent applications (in particular, a paper by Rich), although not considered by the Examiner to be sufficient to cause an "obviousness" rejection might be challenged in litigation. After consultation with the Examiner, the Applicant has divided the material in the original claims to create narrower claims.

The Applicant will file the appropriate terminal disclaimers for any claims allowed.

For antecdents for Claim 11, see Claim 1 of USP 6001983 , and supporting disclosure in the specification.

For antecdents for Claim 21, see Claim 1 of USP 5432272, and supporting disclosure in the specification, USP 5965364 column 2, line 53ff for enzymes suitable for the polymerase chain reaction. The abstracts do not disclose this art.

For antecdents for Claim 21, see Example 2 (Column 10) of USP 5432272,

Sincerely yours,

Steven A. Benner
(Applicant)